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No. 03-1237

In the Supreme Court of the United States

MERCK KGaA, PETITIONER

v.

INTEGRA LIFESCIENCES I, LTD., ET AL.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE

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QUESTION PRESENTED

Under 35 U.S.C. 271(e)(1), it is generally not an act of infringement to use a patented invention "solely for uses reasonably related to the development and submission of information under a Federal law" regulating the manufacture, use, or sale of drugs. The question presented is whether the court of appeals erred in limiting that exemption to clinical studies designed to provide information for Food and Drug Administration approval of a new drug.

TABLE OF CONTENTS

	Page
Statement	1
Discussion	8
I. The decision below misconstrues the scope of the FDA exemption	8
II. Review is warranted at this time	15
Conclusion	20

TABLE OF AUTHORITIES

Cases:

Eli Lilly & Co. v. *Medtronic, Inc.*, 496 U.S. 661 (1990)	7, 8, 11, 12, 19
Integra LifeSciences I, Ltd. v. *Merck KgaA*, No. 96 CV 1307-B(AJB), 2004 WL 2284001 (S.D. Cal. Sept. 7, 2004)	8, 17, 18
Intermedics, Inc. v. *Ventritex, Inc.*, 775 F. Supp. 1269 (N.D. Cal. 1991), aff'd, 991 F.2d 808 (Fed. Cir. 1993)	5, 16
Madey v. *Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002), cert. denied, 539 U.S. 958 (2003)	4

Statutes and regulations:

Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, § 202, 98 Stat. 1585	1
Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 301 *et seq.*	2
21 U.S.C. 355(a)	2, 9
21 U.S.C. 355(d)	2, 9
21 U.S.C. 355(i) (2000 & Supp. I 2001)	2
21 U.S.C. 355(i)(1) (2000 & Supp. I 2001)	9
21 U.S.C. 355(i)(1)(A)	9, 10
21 U.S.C. 355(i)(3)(B)(i)	2
35 U.S.C. 271(a)	1
35 U.S.C. 271(e)(1)	1, 2, 8

Regulations—Continued:	Page
21 C.F.R.:	
Sections 312.20 *et seq.*	9
Section 312.22(b)	9
Section 312.23(a)(3)(iv)	10
Section 312.23(a)(5)(ii)	10
Section 312.23(a)(8)	2, 10
Miscellaneous:	
FDA, Benefit *vs.* Risk: *How CDER Approves New Drugs* (visited Nov. 30, 2004) <http://www.fda.gov/cder/about/whatwedo/testtube-5.pdf>	10
FDA, *Guidance for Industry Exposure-Response Relationships—Study Design Data, Analysis, and Regulatory Applications* (Apr. 2003) <http://www.fda.gov/cder/gdlns/exposure.htm>	10
FDA, *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (Mar. 2004) <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>	13
FDA, *Manual of Policies and Procedures Center for Drug Evaluation and Research, INDs: Screening INDs* (2001) <http://www.fda.gov/cder/mapp/6030-4.pdf>	14
H.R. Rep. No. 857, 98th Cong., 2d Sess. Pt. 1 (1984)	15
NCI, *Clinical Trial Results Progress in Cancer Care* (visited Nov. 30, 2004) <http://clinicatrials.nci.nih.gov/clinicaltrials>	11

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This brief is submitted in response to the order of this Court inviting the Acting Solicitor General to express the views of the United States. The United States believes that the Court should grant the petition.

STATEMENT

1. Under the Patent Act, "whoever without authority makes, uses, offers to sell, or sells any patented invention * * * during the term of the patent therefor, infringes the patent." 35 U.S.C. 271(a). As part of the Drug Price Competition and Patent Term Restoration Act of 1984 (the 1984 Act), Pub. L. No. 98-417, § 202, 98 Stat. 1585, Congress enacted an exemption to that rule:

> It shall not be an act of infringement to make, use, offer to sell, or sell * * * a patented invention * * * solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.

35 U.S.C. 271(e)(1) (the FDA exemption).

The Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 301 *et seq.*, is one such law "regulat[ing] the manufacture, use, or sale of drugs." 35 U.S.C. 271(e)(1). Drug manufacturers typically submit information to the Food and Drug Administration (FDA) at least twice in the course of bringing a drug to market. A manufacturer first submits an investigational new drug application (IND) seeking authorization to conduct clinical trials (*i.e.*, trials on humans) in order to investigate the safety and effectiveness of the drug. See 21 U.S.C. 355(i) (2000 & Supp. 2001); 21 C.F.R. 312.20. In determining whether to permit clinical trials to proceed, the FDA considers whether "the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation." 21 U.S.C. 355(i)(3)(B)(i). The FDA typically considers pre-clinical research, including "pharmacological and toxicological studies of the drug involving laboratory animals or in vitro," in making this evaluation. 21 C.F.R. 312.23(a)(8).

If human clinical trials are successful, a manufacturer then proceeds to the second stage of the FDA review process by submitting a new drug application (NDA) seeking approval to market the drug. See 21 U.S.C. 355(a). The FDA may approve a drug for marketing only if the applicant has shown, based on the results of adequate tests performed by all methods reasonably applicable, that the drug is both safe and effective. 21 U.S.C. 355(d).

2. Respondent Integra LifeSciences I, Ltd., owns patents related to the mechanisms by which cells attach and detach from certain proteins of the extracellular matrix. The extracellular matrix is a type of tissue—such as connective tissue—to which many types of cells adhere. The inventors isolated the particular sequence of amino acids (the RGD peptide) in the protein of the matrix at which cells attach, and also isolated a key receptor—now called $\alpha_v\beta_3$—on the

surface of cells by which the cells attach to the matrix. See generally Pet. App. 4a-5a.

Dr. David Cheresh, a scientist at The Scripps Research Institute (Scripps), which is partially funded by petitioner, determined that $\alpha_v\beta_3$ is involved in angiogenesis, the process of blood vessel proliferation by which tumors in the body obtain blood that allows them to grow. Cheresh also found that an RGD peptide provided by petitioner, denoted EMD 66203, inhibited $\alpha_v\beta_3$ receptors, and that blocking this cell surface receptor could stop angiogenesis. It might also treat diabetic retinopathy, rheumatoid arthritis, psoriasis, and inflammatory bowel disease. Pet. App. 5a.

Based on those results, petitioner entered into a new agreement with Scripps in 1995 to fund "necessary experiments to satisfy the biological bases and regulatory (FDA) requirements for the implementation of clinical trials." Pet. App. 4a-5a. Under the agreement, "compounds designed and synthesized at E. Merck [would] be directly tested at Scripps" for "half-life, toxicity and efficacy." C.A. App. 10,099. The agreement contemplated that clinical trials would begin within three years, under the auspices of Merck. *Id.* at 10,100, 10,108.

The ensuing experiments identified two other derivatives of EMD 66203 that appeared to be even more promising: EMD 85189 and EMD 121974. Pet. App. 5a. Animal and other pre-clinical testing continued on all three peptides:

> Scripps scientists conducted several *in vivo* and *in vitro* experiments "to evaluate the specificity, efficacy, and toxicity of EMD 66203, 85189 and 121974 for various diseases, to explain the mechanism by which these drug candidates work, and to determine which candidates were effective and safe enough to warrant testing in humans."

Id. at 5a-6a; see C.A. App. 11,001-11,003 (listing accused experiments).

In 1997, Scripps determined that EMD 121974 was the best candidate for drug development. Pet. App. 6a. In 1999, the National Cancer Institute (NCI) filed an IND for EMD 121974. *Id.* at 28a (Newman, J., concurring in part and dissenting in part).

3. In 1996, while this research was progressing, respondents brought suit against petitioner for patent infringement. Respondents claimed, *inter alia*, that Cheresh and Scripps infringed various patents relating to the RGD peptide, and that petitioner willfully infringed the patents by partially funding the research and supplying certain peptides and cell receptors (including $\alpha_v\beta_3$) to Cheresh and Scripps. Petitioner defended based in part on two exemptions to patent infringement. Petitioner argued that the research conducted before 1995 was "basic research" exempt under the common law "experimental use" exemption. See *Madey* v. *Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002), cert. denied, 539 U.S. 958 (2003). Petitioner argued that the remainder of the research was exempt under Section 271(e)(1).

4. The district court entered a judgment of infringement against petitioner. Pet. App. 45a-46a. The district court ruled that all but one of the experiments undertaken before 1995 qualified as "basic research" and thus were exempt. See *id.* at 35a (Newman, J., dissenting in part). But the court submitted petitioner's FDA exemption defense to the jury, and instructed the jury as follows:

> To prevail on this defense, Merck must prove by a preponderance of the evidence that it would be objectively reasonable for a party in Merck's and Scripps' situation to believe that there was a decent prospect that the accused activities would contribute, relatively directly, to the generation of the kinds of information that are likely to be relevant in the processes by which the FDA would decide whether to approve the product in question.

Id. at 39a. Petitioner did not seek to refine that instruction. The jury returned a general verdict that petitioner, Scripps, and Cheresh infringed respondents' patents, and that the FDA exemption was not applicable. C.A. App. 170-171. The jury awarded $15 million in damages. Pet. App. 4a.

Respondents asked the district court to treble the damages due to the alleged willfulness of the infringement. The district court rejected that request, and explained that "the FDA Exemption is written in terms which make it difficult for a scientist to know when he or she is or is not within the exemption." Pet. App. 40a. "Additionally," the court continued, "much of the evidence at trial established that the accused experiments generated the types of information that are submitted to the FDA." *Ibid.* The district court denied, however, petitioner's motion for judgment as a matter of law on the FDA exemption. *Id.* at 48a-49a.

5. A divided panel of the Federal Circuit affirmed the district court's liability ruling. Pet. App. 4a, 8a-14a. The majority noted that because the "focus of the entire exemption is the provision of information to the FDA," an "otherwise infringing activity must reasonably relate to the development and submission of information for FDA's safety and effectiveness approval process" in order to qualify for the exemption. *Id.* at 11a. According to the panel, Section 271(e)(1) "simply does not globally embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process." *Id.* at 13a.

Instead, the court of appeals held that "the district court correctly confined the § 271(e)(1) exemption to activity that 'would contribute (relatively directly)' to information the FDA considers *in approving a drug.*" Pet. App. 13a (quoting *Intermedics, Inc.* v. *Ventritex Co.*, 775 F. Supp. 1269, 1280 (N.D. Cal. 1991), aff'd, 991 F.2d 808 (Fed. Cir. 1993) (Table))

(emphasis added). The panel reasoned that the FDA "has no interest in the hunt for drugs that may or may not later undergo *clinical testing for FDA approval*," and "does not require information about drugs other than the compound featured in an Investigational New Drug application." *Id.* at 12a (emphasis added).

The court thereby drew a distinction between clinical and pre-clinical research, and repeatedly indicated that pre-clinical research does not qualify for the exemption. See, *e.g.*, Pet. App. 12a ("the Scripps work sponsored by Merck was not 'solely for uses reasonably related' to *clinical testing* for FDA") (emphasis added); *id.* at 10a (identifying "the question arising in this case" as being "whether the *pre-clinical research* conducted under the Scripps-Merck agreement is exempt from liability") (emphasis added); *id.* at 12a ("the Scripps work sponsored by Merck was not *clinical testing* to supply information to the FDA") (emphasis added). Similarly, the court indicated that the statutory exemption extends only to information relevant to ultimate "FDA approval" of a new drug (*id.* at 12a, 13a), confirming its conclusion that Section 271(e)(1) is limited to the type of clinical research required to obtain such approval. See *id.* at 13a (exemption "confined" to "information the FDA considers in *approving* a drug") (emphasis added).

The court of appeals relied heavily on legislative history suggesting that "the express objective of the 1984 Act was to facilitate the immediate entry of safe, effective generic drugs." Pet. App. 12a; see *id.* at 9a. In the court's view, "the context of this safe harbor" demonstrates a focus on "facilitating expedited approval of" generic versions of patented drugs "already on the market." *Id.* at 13a.

After affirming as to liability, the court of appeals reversed the jury's $15 million damages award as excessive. Pet. App. 17a-22a. The court remanded for the district court to award damages based on "the results of a hypothetical

negotiation between the patentee and the infringer at a time before the infringing activity began." *Id.* at 18a (citation omitted). The court observed that the calculation of a reasonable royalty would be affected by a number of factors, including "the date on which the hypothetical negotiation in advance of infringement would have occurred" and "the time point at which Merck utilized RGD peptides in its drug development process." *Id.* at 18a, 22a.

Judge Newman dissented from the liability determination. Pet. App. 24a-35a. In her view, all of Cheresh's experiments are exempt under either the FDA exemption or the common law experimental use exemption. *Id.* at 35a. Judge Newman noted that this Court has interpreted Section 271(e)(1) to have a "broader scope" than generic drugs. *Id.* at 32a (citing *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661 (1990)). Although she agreed with the majority that the FDA exemption does not "reach back down the chain of experimentation to embrace development and identification of new drugs," Judge Newman determined that all of the research at issue "was either exempt exploratory research, or was immunized by § 271(e)(1)." *Id.* at 33a. "It would be strange," she explained, "to create an intervening kind of limbo, between exploratory research subject to exemption, and the FDA statutory immunity, where the patent is infringed and the activity can be prohibited." *Ibid.*

The Federal Circuit denied rehearing and rehearing en banc. Pet. App. 54a. At the same time, the panel issued an "errata" sheet stating that the "scope of the safe harbor is not limited to generic drug approval" but that nonetheless "the history of the 1984 Act" as described by the panel "informs the breadth of the statutory test." *Id.* at 36a. The panel also made related edits to its opinion, but did not

change the portions of its opinion indicating that only clinical studies are covered by the FDA exemption.[1]

DISCUSSION

The decision of the court of appeals reflects an incorrect view of the law, and is likely to restrict significantly the development of new drugs. Fairly read, the decision below holds that "pre-clinical" research regarding a potential new drug is not protected by the FDA exemption because that exemption is limited to "clinical" research necessary to obtain ultimate FDA approval of a new drug. That holding is inconsistent with the text of the FDA exemption, reflects a mistaken and unduly narrow view of the types of information relevant to the FDA's two-step process for evaluating potential new drugs, and is in tension with this Court's decision in *Eli Lilly & Co.* v. *Medtronic, Inc.*, 496 U.S. 661 (1990). Moreover, the court of appeals' decision poses a direct and substantial threat to new drug research by dramatically narrowing the scope of protections enacted by Congress in Section 271(e)(1). Although this case is not an ideal vehicle for considering the issue, see p. 18, *infra*, the potential impact of the court of appeals' legal conclusion is sufficiently important that the petition for a writ of certiorari should be granted.

I. THE DECISION BELOW MISCONSTRUES THE SCOPE OF THE FDA EXEMPTION

Under 35 U.S.C. 271(e)(1), use of a patented invention "solely for uses reasonably related to the development and

[1] On remand, the district court determined that the hypothetical negotiation would have occurred in August 1994 because the first infringing experiment occurred at that time. *Integra LifeSciences I, Ltd.* v. *Merck KGaA*, No. 96 CV 1307-B(AJB), 2004 WL 2284001, at *5-6 (S.D. Cal. Sept. 7, 2004). The court also found $1.5 million per year to be a reasonable royalty, prorated by month, and awarded damages of $6.375 million based on its determination that infringement began in August 1994 and ended in November 1998. *Id.* at *11.

submission of information under a Federal law which regulates the manufacture, use, or sale of drugs" is exempt from liability for patent infringement. The plain language of the drug laws and regulations, and the policy behind the FDA exemption, establish that at least some research conducted prior to filing an IND with the FDA falls within the scope of Section 271(e)(1).

a. Congress expressly contemplated that pre-clinical studies would be submitted to the FDA. Under the FFDCA, a new drug intended for human use cannot be introduced into interstate commerce until the Secretary of Health and Human Services has determined that it is both safe and effective. 21 U.S.C. 355(a) and (d). In order to facilitate clinical testing of new drugs that have not yet been found to satisfy those requirements, Congress has exempted from the pre-market safety and effectiveness requirements "drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs." 21 U.S.C. 355(i)(1) (2000 & Supp. I 2001). Congress authorized the Secretary to promulgate regulations "conditioning such exemption upon * * * the *submission to the Secretary * * * of preclinical tests (including tests on animals)* of such drug adequate to justify the proposed clinical testing." 21 U.S.C. 355(i)(1)(A) (emphasis added).

Pursuant to that statute, the Secretary promulgated regulations establishing the investigational new drug application process. See 21 C.F.R. 312.20 *et seq.* Those regulations do not require any specific studies (see 21 C.F.R. 312.22(b)), but they expressly contemplate the submission of pre-clinical experiments as part of an IND. Thus, the regulations require a "summary of the pharmacological and toxicological effects of the drug in animals," "[a]dequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro," and explanation of

the "rationale for the drug or the research study." 21 C.F.R. 312.23(a)(3)(iv), (5)(ii) and (8). Data from pre-clinical research typically provide essential support for those elements.

Pre-clinical studies related to the effectiveness of a drug are also considered by FDA at the IND stage in assessing whether the potential benefits of a drug outweigh any possible safety risks. See 21 U.S.C. 355(i)(1)(A) (charging FDA with balancing need for human testing with safety of patients). Based on the results of such studies, FDA might allow clinical testing of a drug that poses significant safety concerns if the drug has sufficiently positive potential to address a serious disease or condition, although the agency would not accept similar risks for a drug to treat a less serious medical condition. See generally FDA, Benefit *vs.* Risk: *How CDER Approves New Drugs* (visited Nov. 30, 2004) <http://www.fda.gov/cder/about/whatwedo/testtube-5.pdf>.

For all of those reasons, data from pre-clinical research are routinely submitted in INDs to FDA, and considered by FDA as part of its review. As FDA has explained, "[m]any drugs thought to be of potential value in treating human disease are introduced into development based on knowledge of in vitro receptor binding properties and identified pharmacodynamic effects in animals." FDA, *Guidance for Industry Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications* (Apr. 2003) <http://www.fda.gov/cber/gdlns/exposure.htm>.

This case is illustrative of that practice. NCI, a component of the National Institutes of Health (NIH), filed an IND for EMD 121974, now called cilengitide, proposing to run a clinical trial to assess the compound's safety and cancer-fighting abilities. See Pet. App. 28a (Newman, J., dissenting); C.A. App. 29. According to NCI, at least some of the pre-clinical experiments conducted by Cheresh were included in the IND because they relate to the effectiveness of

the cancer-fighting properties of the drug.[2] Some of the same pre-clinical experiments were also included in another cancer-related IND filed by a different company. 21 Tr. 3059-3060 (testimony that data from chick experiments, in vitro experiments, rabbit cornea experiments, and mouse experiments were included in IND submitted by Ixsys). FDA received and found acceptable the IND for cilengitide, and currently NCI is sponsoring numerous clinical trials to test the safety and effectiveness of cilengitide against various forms of cancer. See NCI, *Clinical Trial Results —Progress in Cancer Care* (visited Nov. 30, 2004) <http://clinicaltrials.nci.nih.gov/clinicaltrials>.

Because Congress expressly contemplated that the FDA would consider pre-clinical research in reviewing INDs, and the FDA does in fact consider such research, as shown by both its regulations and its settled practice, there can be little doubt that at least some experiments that occur before the clinical phase are "reasonably related" to the submission of information to FDA. Though not dispositive, the fact that some of the pre-clinical experiments at issue here were included in submissions to FDA further illustrates that point.

b. The policy concerns animating the FDA exemption also counsel against limiting the exemption to clinical research. As this Court explained in *Medtronic*, 496 U.S. at 670, Congress enacted the FDA exemption because "the combined effect of the patent laws and the premarket regulatory approval requirement was to create an effective extension of the patent term" by preventing competitors from undertaking tests necessary to obtain FDA approval until after a patent expired. Congress intended the FDA exemption to eliminate that delay by "allow[ing] competitors, prior

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[2] The IND filed by NCI at the request of petitioner was excluded from evidence in this case because it "was improperly withheld from discovery." C.A. App. 29. We rely on it here solely to illustrate the FDA's practice and the government's interest in this type of data.

to the expiration of a patent, to engage in otherwise infringing activities necessary to obtain regulatory approval." *Id.* at 671.[3]

That congressional policy is every bit as relevant to the types of pre-clinical studies that support INDs as it is to the clinical studies that support NDAs. In this case, permitting research involving the patented invention to occur prior to the expiration of respondents' patent would facilitate the marketing of a promising cancer-fighting drug to the public as soon as the patent expires.

The court of appeals expressed a considerably different (and incorrect) view of the policies animating the Act. Based on a review of the legislative history, the court determined (Pet. App. 12a, 13a) that Section 271(e)(1) should be read narrowly because "the express objective of the 1984 Act was to facilitate * * * generic drugs." *Id.* at 12a. That reasoning is incorrect: in *Medtronic*, 496 U.S. at 665-667, 669 n.2, this Court rejected the contention that the 1984 Act's legislative history requires that Section 271(e)(1) be limited to generic drugs, and held that even medical devices are covered.

Although the court of appeals issued an "errata" sheet indicating that "the scope of the safe harbor is not limited to generic drug approval," Pet. App. 36a, the revised opinion continues to hold that the statutory exemption should be construed to focus primarily on generic drugs, and appears to adopt the view that the exemption does not encompass pre-clinical studies prepared for an IND. See *id.* at 12a-13a. In particular, the decision holds that the exemption is "confined" to "information the FDA considers in *approving* a

[3] The FDA exemption does not reduce the amount of time the patent holder is statutorily entitled to exclude others from the marketplace. It merely assures that once the patent expires, competitors will be able to compete without further delay, such that the effective period of exclusivity is not the statutory patent term *plus* the time necessary for a competitor to obtain regulatory approval.

drug," and therefore applies only to work "'reasonably related' to *clinical* testing for FDA," as opposed to the "pre-clinical research" conducted here. *Id.* at 10a, 12a, 13a (quoting 35 U.S.C. 271(e)(1)) (emphases added); see pp. 5-6, *supra*. Thus, the court of appeals incorrectly narrowed the statutory exemption, based in part on a mistaken view of congressional intent that this Court has already rejected.

c. To be sure, not all research that occurs before the commencement of the clinical phase will necessarily fall within the FDA exemption. As all three judges on the court of appeals noted, Section 271(e)(1) does not reach all the way down the causal chain to "embrace all experimental activity that at some point, however attenuated, may lead to an FDA approval process." Pet. App. 13a; accord *id.* at 33a. Thus, the initial stages of basic exploratory research may not be covered by Section 271(e)(1). But at the very least, when a company identifies a particular compound or a small number of analogs for pre-clinical research with an eye toward submitting an IND, the ensuing research is reasonably related to the development and submission of information to the FDA. Indeed, the latter category of research is as relevant to an IND as clinical trials are to an NDA, and Section 271(e)(1) applies by its terms to the development and submission of information under *any* federal law regulating the manufacture, use, or sale of drugs.

The distinction between basic research and pre-clinical studies relevant to a potential IND is not a difficult line for courts to police, because it is well rooted in industry and regulatory practice. Indeed, the FDA has identified basic research, prototype design or discovery, preclinical development (typically involving in vitro and animal testing and modeling), clinical development (typically including human testing), and FDA approval as distinguishable steps in the drug development process. See FDA, *Innovation/ Stagnation: Challenge and Opportunity on the Critical Path to*

New Medical Products 4, 10 (Mar. 2004) (Figs. 4, 6) <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf>.

The court of appeals suggested (Pet. App. 12a) that research into more than one substance should be considered non-exempt, basic research because, in the court's view, "the FDA does not require information about drugs other than the compound featured in an Investigational New Drug application." Although the FDA does not require *any* particular experiments as a prerequisite to approving an IND, see p. 9, *supra*, the agency does consider research into close analogs of a compound in making its determination. From FDA's perspective, the question is not whether an experiment involves the "featured" compound or a derivative, but whether the research helps demonstrate that the potential drug is sufficiently promising to warrant the risks of a clinical trial. Research on derivative compounds can help to demonstrate the effectiveness of a drug.

Research of close analogs is sufficiently common that the FDA has developed a procedure, called a Screening IND, to permit a drug company to present several variants of a drug in a single IND, with a view toward researching "a number of closely related drugs to choose the preferred compound or formulation." FDA, *Manual of Policies and Procedures, Center for Drug Evaluation and Research, INDs: Screening INDs* 1 (2001) <http://www.fda.gov/cder/mapp/6030-4.pdf>; see *id.* at 3 (explaining that screening INDs are generally appropriate for testing five or fewer closely related compounds). There is no basis for excluding such research from the scope of Section 271(e)(1).

To the contrary, Section 271(e)(1) expressly covers all uses "reasonably related to the development and submission of information" under the FFDCA, and thus extends to research reasonably calculated to lead to the submission of an IND, even if the research ultimately is unsuccessful and

no IND is submitted for the compound in question. As the legislative history of the 1984 Act makes clear:

> A party which develops such information, but decides not to submit an application for approval, is protected as long as the development was done to determine whether or not an application for approval would be sought.

H.R. Rep. No. 857, 98th Cong., 2d Sess. Pt. 1, at 45 (1984). Any other interpretation would unacceptably chill innovation and new drug development, as researchers would be unable to ascertain in advance whether their activities would be protected by the exemption.

II. REVIEW IS WARRANTED AT THIS TIME

The Federal Circuit's erroneous decision warrants further review because, contrary to respondents' claims (Br. in Opp. 6-7, 14-15), the decision is not unduly fact-bound, and the legal conclusion embraced by the Federal Circuit is likely to reduce the amount of socially valuable and necessary pre-clinical new drug research.

a. Although respondents contend (Br. in Opp. 2) that the court of appeals "simply recognized that the statute * * * presents a factual issue to the jury," and "held that sufficient evidence supported the jury's factual determination," nothing in the court's opinion supports that statement. The court of appeals did not premise its decision on the jury verdict (which it also disregarded on the calculation of damages), but instead affirmed the district court's judgment on the erroneous legal ground that Section 271(e)(1) protects "clinical" research, not the "pre-clinical" research conducted by petitioner in this case. See pp. 5-6, 12-13, *supra*. While respondents are correct (Br. in Opp. 5) that the *district court* stated that the case turns on the jury's resolution of factual disputes, it is the court of appeals' holding, not the district

court's, that currently chills the activities of drug researchers and binds every drug manufacturer in the nation.[4]

Respondents also err (Br. in Opp. 9) in relying on the Federal Circuit's characterization of petitioner's research as "general biomedical research to identify new pharmaceutical compounds." Pet. App. 12a. The court of appeals made clear that petitioner had undertaken "pre-clinical" research limited to "EMD 66203 or a derivative thereof," and that the research included "necessary experiments to satisfy the biological bases and *regulatory (FDA) requirements for the implementation of clinical trials.*" *Id.* at 5a (citation omitted) (emphasis added); see *id.* at 10a. Thus, the basic search was over, and the preparation for clinical trials had begun. Regardless of whether one characterizes this research as "general," at least some of it was clearly related to the development and submission of information to FDA under the FFDCA, and therefore protected by Section 271(e)(1) as a matter of law.[5]

[4] The district court held (Pet. App. 48a-49a) that the jury could permissibly rely in part on "expert" testimony that FDA's responsibility is limited to safety, and that the relevant pre-clinical research had nothing to do with safety. To the contrary, however, FDA's responsibility includes both safety and effectiveness, and FDA is interested in reviewing the types of data generated here. See pp. 9-10, *supra*. The district court also concluded (Pet. App. 49a) that the jury could "disregard as not credible Dr. Cheresh's testimony that the infringing experiments performed at Scripps were done for FDA purposes." The correct legal standard is an *objective* one, however, and should frequently be subject to resolution as a matter of law. See, *e.g.*, *Intermedics*, 775 F. Supp. at 1280. Moreover, the district court erred in relying on petitioner's admission that the particular research studies at issue were not "necessary" to the development of petitioner's peptides. Pet. App. 49a. The question under the statute is merely one of reasonable relationship. Because no particular experiments are required for purposes of an IND, a "necessity" test (as opposed to a "reasonable relationship" test) could improperly exclude all pre-clinical research.

[5] Just as this case does not involve only basic research, it has nothing to do with "research tools." Pet. App. 14a. As Judge Newman observed, there is an obvious difference between the use of a substance as a tool to study other substances, and the study of the substance itself. *Id.* at 35a (dissenting opinion). Here, the "Scripps/Merck syntheses and evaluations of new RGD peptides" did not amount to "use of the Integra products as a research tool." *Ibid.*

Even if some of the challenged experiments could properly be viewed as infringing, reversal and remand for application of the correct legal standard would likely affect the result on remand by affecting the quantum of damages. The Federal Circuit remanded to the district court for further consideration of damages (Pet. App. 22a), and explained that because damages should be based on "the results of a hypothetical negotiation between the patentee and the infringer at a time before the infringing activity began," the "first step in a reasonable royalty calculation is to ascertain the date on which the hypothetical negotiation in advance of infringement would have occurred." *Id.* at 18a. The court further noted that "the time point at which Merck utilized RGD peptides in its drug development process" could play a role in the royalty calculation. *Id.* at 22a. The damages calculation, therefore, requires a focus on whether specific research projects involved infringing uses, and the proper scope of the FDA exemption should prove relevant to that issue.

On remand, the district court determined that the hypothetical negotiation would have occurred in August 1994 because the first infringing experiment occurred at that time, and further found that the infringement lasted from August 1994 until November 1998. *Integra LifeSciences I, Ltd.* v. *Merck KGaA*, No. 96 CV 1307-B(AJB), 2004 WL 2284001, at *5-6, 11 (S.D. Cal. Sept. 7, 2004). The court also found $1.5 million per year to be a reasonable royalty. *Id.* at *11. Accordingly, the court applied that annual royalty rate, prorated by month, to the full period of alleged infringement and awarded damages of $6.375 million. *Ibid.*

Because that damages calculation depends upon the specific time period during which infringing conduct occurred, a

determination that at least some of the challenged experiments were protected as a matter of law by Section 271(e)(1) would likely affect the damages award. Indeed, the district court found that "[i]n 1997, the Scripps research team chose EMD 121974 as the best candidate for clinical development," 2004 WL 2284001, at *3, and asserted that "the preclinical phase of the Merck drug development program" commenced in 1997. Pet. App. 49a. Thus, even under the district court's view of the evidence, it appears that the experiments undertaken after 1997 were exempt under the correct legal standard, and no damages should have been awarded based on those experiments.

b. To be sure, this case is not an ideal vehicle for considering the question presented. Petitioner did not seek to refine the jury instruction in this case, and this Court could reverse the Federal Circuit's erroneous legal holding based on a test that would not necessarily lead to a reversal of the finding of liability, although petitioner's theory could certainly lead to that result. Moreover, although it appears likely, as discussed above, that application of the correct legal standard would affect the damages calculation under the model employed by the district court, the court of appeals has not yet had occasion to review the district court's ruling on damages. Although those considerations weigh against review, the exercise of certiorari jurisdiction remains warranted here because of the immediate adverse impact that the court of appeals' decision is likely to have on important medical research, an impact that is magnified by the Federal Circuit's exclusive national jurisdiction over patent appeals.

Although the patent system provides important incentives for innovation, pre-clinical research into investigational new drugs is of tremendous importance to the public health, and the decision below so substantially shrinks the FDA exemption that it cannot help but impede such research.

Under the Federal Circuit's decision, a manufacturer aware of a promising new cure involving a patented invention could not undertake the pre-clinical studies needed to secure FDA permission to conduct clinical studies, which in turn are required for FDA approval of a new drug. That cramped reading deprives Section 271(e)(1) of much of its value, and effectively extends the terms of such patents well beyond their expiration dates, frustrating a key purpose of the 1984 Act. See *Medtronic*, 496 U.S. at 670.

Although petitioner overreaches in claiming (Pet. 4) that the decision below has "transformed" the United States "into hostile territory for drug innovation," the affected federal agencies, including FDA and NIH, believe that the court of appeals' decision is likely to restrict significantly the development of new drugs. Indeed, FDA is aware of anecdotal evidence that the court of appeals' decision is already adversely affecting the legal advice given to drug researchers regarding their ability to use patented inventions in new drug research.

Respondents emphasize (Br. in Opp. 15) that drug manufacturers can attempt to negotiate license agreements with patent holders. If licensing were always a realistic solution, however, Section 271(e)(1) would be altogether unnecessary, because a researcher could always license any patented technology. Moreover, licensing would require researchers to pay for uses that Congress deemed not infringing. Even if the possibility of licensing will not stop research in its tracks, it will increase the cost and thus decrease the level of such research relative to what Congress intended. In enacting the FDA exemption, therefore, Congress necessarily rejected respondents' view that the potential for licensing adequately protects the public health.

That congressional judgment was a reasonable one, because there are serious impediments to obtaining a license in many cases. For competitive reasons, a drug company might

be unwilling to license patented technology to a competitor, even when, as here, the patent holder is unable to convert the patented technology into a useful drug. A patent holder willing to enter into a license might demand an unreasonable fee, or a researcher might be unable or unwilling to pay a substantial fee in light of the speculative and costly nature of drug research. For all of those reasons, the court of appeals' restrictive interpretation of Section 271(e)(1) will likely hinder the development of important and medically valuable new drugs.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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